REMARKS

I. STATUS OF CLAIMS

Claims 1-37 are pending in this application. Claims 1-12, 15-17, 19, 26, 28, 29, 31, and 33-37 are withdrawn from consideration as directed to non-elected subject matter. Claims 13, 14, 18, 20-25, 27, 30, and 32 are under examination and stand rejected. Claims 13, 21 and 30 are amended herein to further define the subject matter being claimed. For example, claim 13 is amended to further define "(i)," wherein R^1 and R^2 form together a six-membered ring, and R^2 and R^3 form together a five-membered ring. Support for this amendment is found, for example, in the substitute specification at page 25, ll. 8-11. Claim 21 is amended to delete compound "AF." Claim 30 is amended to explicitly state what was implicit before, that a double is present between Z' and Z" for formula 1(I).

Accordingly, no new matter has been added by the above amendments.

II. ELECTION OF SPECIES REQUIREMENT

The Examiner finalizes the Election of Species Requirement dated February 23, 2009. Office Action at page 2. While the Examiner states that the election of species "1(T)" was made in response to the Election of Species Requirement mailed February 23, 2009, Applicants note that the elected species made in the Response submitted August 21, 2009, is "1(O)." *Id.* at page 2. Clarification on the record is therefore respectfully requested.

Applicants continue to respectfully traverse the Election of Species Requirement and disagree with the Examiner's comments in support of the Requirement, for the reasons of record and for the following additional reasons.

In particular, the Examiner's pending election requirement contravenes the purpose of groups reciting alternative elements, which deems such groups proper if they present no uncertainty or ambiguity with respect to the question of scope or clarity of the claims. *See Ex parte Markush*, 1925 C.D. 126 (Comm'r Pat. 1925). The proper standard to apply in the instant situation is found at M.P.E.P. § 803.02. The M.P.E.P. instructs:

> If the members of the Markush group are sufficiently few in number or so closely related that a search and examination of the entire claim can be made without serious burden, **the examiner must examine all the members of the Markush group in the claim on the merits, even though they are directed to independent and distinct inventions.** In such a case, the examiner will not follow the procedure described below and will not require restriction.
>
> Since the decisions in In re Weber, 580 F.2d 455, 198 USPQ 328 (CCPA 1978) and In re Haas, 580 F.2d 461, 198 USPQ 334 (CCPA 1978), it is improper for the Office to refuse to examine that which applicants regard as their invention, unless the subject matter in a claim lacks **unity of invention**. In re Harnish, 631 F.2d 716, 206 USPQ 300 (CCPA 1980); and Ex parte Hozumi, 3 USPQ2d 1059 (Bd. Pat. App. & Int. 1984). **Broadly, unity of invention exists where compounds included within a Markush group (1) share a common utility, and (2) share a substantial structural feature disclosed as being essential to that utility.**

M.P.E.P. § 803.02 (emphasis added).

The compounds of the invention satisfy the above two-prong test for unity of invention. First, the instantly-claimed compounds share a common utility, i.e., compounds intended to treat HCV infections. Substitute Specification at page 13, ll. 15-20. Second, the compounds share a substantial structural feature (i.e., they are all bicyclo[4.2.1]nonane rings derived from nucleosides), which is essential to the aforementioned common utility.

Moreover, the Examiner is able to restrict two or more inventions that are independent and distinct in one application but the application can have more than one species, not to exceed a reasonable number. In determining a "reasonable" number, historic versions of Rule 141 indicate that the number of species could not exceed five. Therefore, the current version of the Rule with the phrase "a reasonable number" liberalized the limitation. In this case, the restricted claims include sufficiently few species not exceeding a "reasonable" number and hence should be included in a single search and examination. Otherwise, continually limiting examination to an individual species would require Applicants to file applications directed to each individual species causing delay, expense, and duplicative examination.

For at least the foregoing reasons, and in order to avoid unnecessary delay and expense to Applicants and duplicative examination, it is respectfully requested that the Election Requirement be reconsidered.

III. CLAIM OBJECTION

The Examiner objects to claim 30 because "Z' and Z" may be CH, CX, or N, [b]ut the bond in the formula between them appears to be a single bond and no option is provided for a double bond, even though each disclosed option would require a double bond to fill valency." Office Action at page 3.

Applicants respectfully submit that by the definitions recited for Z' and Z", one of ordinary skill in the art would have understood there to be a double bond between Z' and Z" in formula 1(I). As the Examiner correctly notes at page 3 of the Office Action, "each disclosed option would require a double bond to fill valency." Solely to advance prosecution, and without disclaimer or prejudice, Applicants have amended formula 1(I)

in claim 30 to explicitly include a double bond between Z' and Z'' Thus, Applicants respectfully request withdrawal of the objection.

IV. REJECTION UNDER 35 U.S.C. § 103(a)

A. Sasaki and Patani

Claims 13, 14, 18, 20-22, 25, 27, 30, and 32 are rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over Sasaki et al. (J. Org. Chem., 1976, 41 (7), 1100-1104) ("Sasaki") in view of Patani et al. (Chem. Rev. 1996, 3147-3176) ("Patani"). Office Action at page 3. According to the Examiner, "Sasaki et al teaches compound 4 . . . which differs from 1(O) in that two oxygen[s] are substituted on the 3,4-dihydropyrimidin-2(1H)-one ring rather than an oxygen and an amide, as instantly claimed." *Id.* at 4. Relying on Patani, the Examiner contends that "substitut[ing] known isosteres, such as disclosed in the secondary reference," would have been obvious to one of ordinary skill in the art. *Id.* Applicants respectfully traverse this rejection for the following reasons.

The Examiner states that Patani teaches that imines (-C=N-) are bioisosteres of amides (-C=O-) (as in compound 4 of Sasaki). Office Action 4. The Examiner alleges that Patani teaches "the hetero atom leads to tautomerization of these groups." *Id.* The Examiner further contends that "[i]t would be obvious to one ordinary skill in the art . . . to substitute known isosteres," resulting in the tautomers "where the -NH-C(=NH)- [would] resonate[] to NH=C(-NH2)-, as recited in the compound 1(O)." *Id.* Applicants respectfully disagree for at least the reason that the Examiner has provided no reason for selecting a lead compound, or any reason to modify that compound in a particular

way. Moreover, the Examiner has not shown that one making such modifications would expect to succeed in that modification.

The law requires that in an obviousness rejection of a claim to a chemical compound, the Examiner must identify a lead compound that one of ordinary skill in the art would have chosen for further modification. Yet, the Office has provided no reason why one of ordinary skill would have selected the compound in Sasaki chosen by the Office as a lead compound, as required by recent Federal Circuit decisions. Following *KSR Int'l* Co. *v. TeleFlex Inc.,* 127 S.Ct. 1727 (2007), the Federal Circuit has made clear that, "post-*KSR*, a prima facie case of obviousness for a chemical compound still, in general, begins with the **reasoned identification of a lead compound**" in the art. *Eisai* Co. *Ltd. v. Dr. Reddy's Labs.,* Ltd., 533 F.3d 1353, 1357,87 U.8.P.Q.2D (BNA) 1452 (Fed. Cir. 2008) (emphasis added).

The law also requires that once a lead compound has been selected, to the Examiner must show that one of ordinary skill in the art would have made the modifications proposed by the Examiner. *Takeda Chemical Industries, Ltd., v. AlphaPharm Pty, Ltd.*, 492 F.3d 1350, 1356 (Fed. Cir. 2007). However, the Examiner has not shown that the art of record would have suggested making the proposed modification to the compound disclosed in Sasaki. Indeed, the Examiner makes no mention at all of why one of ordinary skill in the art would have been led to make that modification.

The Examiner has identified compound 4 as representative of the scope and contents of Sasaki. However, the Examiner has not provided any reason why compound 4 should be considered a "lead compound." Applicants note that Sasaki

discloses many compounds, but rather than considering the scope and content of Sasaki from the perspective of a person having ordinary skill in the art at the time of the invention, the Examiner focuses on one particular embodiment within the disclosure.

Applicants respectfully point out that using the claims in the instant application as the basis for selecting a "lead compound" from within Sasaki is not permissible. One purpose of requiring the "reasoned identification of a lead compound" is to prevent a compound be chosen as the result of hindsight, which might result in using a claimed compound as a contemporaneous map through the prior art at the time of the invention. The Examiner should consider Sasaki as a whole in order to rationally determine how a person of ordinary skill would have picked a "lead compound" for further investigation at the time of the invention.

A review of Sasaki indicates that compound 4, although capable of converting to compound 3a, has "irregular resonances" leading to "uncertainty" in the interpretation of its NMR interpretation. Sasaki at page 1101. Moreover, Sasaki notes that due to a lack of an analog standard to compare with compound 4, the data was "not sufficient to rule out another possible structure, iii." *Id.* Therefore, Sasaki provides no incentive to one of ordinary skill in the art to pick compound 4, which yielded uncertain results, from any of the other derivatives disclosed.

Moreover, Sasaki reports the synthesis of various 5-bromopyrimidine nucleosides derivatives, but states only that "**some** of the 5-**halo**pyrimidine nucleosides are known to be chemicals of biological interest." Sasaki at page 1100 (emphasis added). Sasaki does not however provide any basis for concluding that any of the derivatives prepared have biological utility. Therefore, the Examiner's assertion that

Sasaki teaches that "[c]ompound 4 has biological activity," is conclusory, and not based on any evidence in Sasaki.

In view of the absence of a valid reason to select the compound of formula 4 of Sasaki, Applicants respectfully submit that the Examiner's contentions regarding the obviousness of isosteric replacement are unsupported. Patani does not supply the missing motivation since that reference indicates only that isosterism is an area of academic development rather than an art-recognized tool for predictably improving on known compounds. Patani describes the field in the introduction: "[t]he concept of bioisosterism is often considered to be qualitative and intuitive." Patani at page 3147. Overall Patani "is focused primarily upon examples . . ." from which the authors make "an attempt to . . . quantitate, in specific instances, physicochemical effects such as electronegativeity, steric size, and lipophilicity . . . to the observed biological activity." *Id.* at page 3148. This description shows that the field of isosterism is limited in its predictive value, better utilized for explaining specific observations with hindsight rather than providing any guidance for how to logically modify a particular compound. Even Patani's teachings are qualified as "an attempt" to draw correlations between molecular structure and function. *Id.*

Despite its limitations, Applicants note that even Patani suggests "modification of lead compounds." Patani at page 3147 (emphasis added). That is, the teachings of Patani may be applicable once one of ordinary skill in the art has identified a suitable compound as a lead compound for modification. As with Sasaki, the Examiner picks the specific replacement of -C=O- with -N=H-, to get to the present claims. Yet, Patani discloses several modifications possible for divalent replacements (-C=C-, -C=N-, -C=O-

, and -C=S-). Therefore, the Examiner has not shown why a person of skill in the art would have chosen the specific replacement of -C=O- by -N=H-, from among all possible modifications described in Patani. Rather than showing that Patani would have suggested the proposed modification to compound 4 of Sasaki, the Examiner asserts that the differences between compound 4 of Sasaki and those of the present claims can be bridged by the teaching of Patani. Office Action at 4 (stating that compound 4 of Sasaki "differs from 1(O) in that two oxygen are substituted on the 3,4-dihydropyrimidin-2(1H)-one ring rather than an oxygen and an amide, as instantly claimed," but that "Patani et al teaches C=O and C=NH are isosteres and their substitution is common in chemical development"). Not only does that statement evidence the Examiner's use of impermissible hindsight, but also of an improper obviousness analysis. Specifically, in a proper obviousness analysis, "the question under 35 U.S.C. 103 is not whether the differences [between the art and the claims] themselves would have been obvious, but whether the claimed invention as a whole would have been obvious." M.P.E.P. § 2141.02(I) (emphasis in original). In the present case, as detailed herein, the claimed invention as a whole would not have been obvious.

The Examiner has not shown why one of ordinary skill in the art would have selected any specific compound from those disclosed in Sasaki for further modification nor why one of ordinary skill in the art would have modified any compound from Sasaki as suggested. Accordingly, the Examiner has not complied with the explicit requirement enunciated in *Takeda* "to identify some reason that would have led a chemist to modify a known compound in a particular manner."

In addition, Applicants respectfully submit that for claims 13, 14, 18, 20, 25, 27, and 30, further modifications of compound 4 of Sasaki are necessary, beyond the specific replacement of -C=O- with -N=H-, in order to get to the compounds recited therein.

For example, amended claim 13 recites that when "R^2 is CR'_2, W is O, $R^{4'}$ is hydroxyl, R^4 is hydrogen, $R^{5'}$ is hydroxyl, and R^5 is hydrogen, the bicyclic ring formed **is not a xanthinyl ring or an 8-azaxanthinyl ring**" (emphasis added). Therefore, compound 4 of Sasaki, which requires an 8-azaxanthinyl ring, would be outside the scope of the pending claims even after it was modified as suggested by the Examiner. Thus, not only does the Examiner's proposed modification (the specific replacement of -C=O- with -N=H-), fail for the reasons discussed above, but it also fails because that modification applies only to a substituent on the 8-azaxanthinyl ring. Consequently, one of ordinary skill in the art would have had no motivation to completely change the structure of compound 4 of Sasaki in order to get to the claimed compounds. Claims 14 and 25, which depend from claim 13, are also nonobvious over Sasaki for the same reasons.

Similarly, compounds 1(A), 1(C), and 1(D) of claim 18, are all distinct from compound 4 of Sasaki because compounds 1(A) and 1(C) contain only one heteroatom on the six-membered ring (in contrast to Sasaki, which requires two heteroatoms), and compounds 1(C) and 1(D) contain only one heteroatom (or possibly two heteroatoms depending upon the definition of "Z") on the five-membered ring (in contrast to Sasaki, which requires three heteroatoms). Regarding compound 1(B), the proviso recited in claim 18 states that "for compounds of formula 1 (B), when X is OH, Y is O, W is O, $R^{4'}$

is hydroxyl, R^4 is hydrogen, $R^{5'}$ is hydroxyl, and R^5 is hydrogen, **Z is not N**" (emphasis added). Therefore, one of ordinary skill in the art would have had to make several modifications of compound 4 of Sasaki, such as removing one heteroatom from the six-membered ring and/or removing at least one heteroatom from the five-membered ring, and/or replacing the nitrogen atom from the Z position, in order to get to the compounds claimed in claim 18. Motivation for these modifications is not present in Sasaki or in Patani. Applicants note that the same reasoning applies for compounds 1(E), 1(F), 1(G), and 1(H) of claim 27.

Nor does the Examiner's reasoning apply to claim 20 at all, as there is no option for an amide substitution on the six-membered ring in the compound recited in claim 20. Moreover, the six-membered ring in compound 4 of Sasaki requires two heteroatoms, in contrast to the compound recited in claim 20, which contains one heteroatom. Thus, because the Examiner has not addressed these apparent differences between the claimed specie in claim 20 and compound 4 of Sasaki, and has not indicated why such substitutions would have been obvious, the Examiner's has failed to make a *prima facie case* of obviousness. Lastly, Applicants note that the same reasoning applies for the compound recited in claim 30, as there is no option for an amide substitution on the six-membered ring in formula 1(I).

In light of these remarks, the Examiner has failed to make a *prima facie* case of obviousness and Applicants respectfully request that this rejection be withdrawn.

B. Sasaki, Patani and Gilbert

Claims 23-24 are rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Sasaki and Patani, and further in view of Gilbert et al. (Antimicrobial

Agents and Chemotherapy, 1986, Vol. 30, No. 2, pp. 201-205) ("Gilbert"). Office Action at page 5. Claims 23 and 24 depend from claim 21. As discussed in Section III.A. above, Sasaki fails to disclose or suggest a composition comprising an effective amount of a compound of claim 21. Gilbert does not remedy this deficiency in Sasaki.

Gilbert is solely focused on the characterization of ribavirin, such as its "chemical structure, possible mode(s) of action, metabolic disposition, and clinical use as an antiviral agent." Gilbert at Introduction. Accordingly, Applicants submit that the rejection is improper and should be withdrawn.

V. CONCLUSION

In view of the foregoing amendments and remarks, Applicants respectfully request reconsideration this application and the timely allowance of the pending claims.

If the Examiner believes a telephone conversation might advance prosecution, the Examiner is invited to call Applicant's undersigned representative at 202-408-4265.

Please grant any extensions of time required to enter this response and charge any additional required fees to Deposit Account No. 06-0916.

Respectfully submitted,

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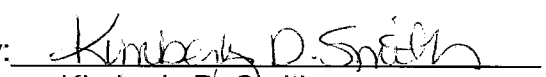
Dated: May 20, 2010

By: 
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